Characteristics of Online Pharmacies Selling Adderall and Rapid-Acting Insulins

By

J. Benjamin Penley

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University of North Carolina at Chapel Hill

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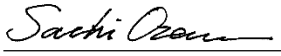

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Abstract

Background

The accessibility from online sources of Adderall (amphetamine/dextroamphetamine), a controlled substance with harmful adverse events if abused or misused, and rapid-acting insulins (Humalog (insulin lispro) and NovoLog (insulin aspart)), high-risk medications with an outsized role in the public debate regarding high drug prices, have not been well documented. There is concern that some patients might choose online pharmacies for a host of reasons, including ease of access, privacy, or cost-savings, unaware that 96% of online pharmacies are illegitimate. Patients who purchase medications from illegitimate online pharmacies remove themselves from traditional healthcare systems that ensure safe and effective drug use. In addition, patients using illegitimate online pharmacies are at risk of receiving low-quality medications.

Objectives

Assess the availability of Adderall, Humalog, and NovoLog from common search engines, and evaluate the safety and marketing characteristics of online pharmacies selling these medications.

Methods

From September 2019 to February 2020, the phrases 'buy Adderall online,' 'buy Humalog online', 'buy NovoLog online', and 'buy insulin online' were queried in four unique search engines. For each query, the first 100 results of Google and Bing, and the first 50 results of Yahoo and DuckDuckGo were screened. Online pharmacies that claimed to sell the queried medication (e.g., Adderall, Humalog, or NovoLog), had unique uniform resource locations (URLs), were active, free-access, and in English language were included. Online pharmacies were categorized as rogue, unapproved, unclassified, or legitimate based on LegitScript classifications. Safety, marketing characteristics, and costs were collected. The analyses of Adderall and rapid-acting insulins (Humalog and NovoLog) were conducted separately.

Results

<u>Adderall</u>

Of 62 online pharmacies found to sell Adderall, 61 were rogue or unclassified. Across all rogue and unclassified online pharmacies, prescriptions were not required (100%), pharmacist services were not offered (100%), and quantity limits were not placed on the number of Adderall units purchased (100%). Rogue and unclassified online pharmacies appealed to cost, claiming price discounts (61%), providing bulk discounts (67%), and offering coupon codes (70%). Contrary to these claims, cheaper prices were available from GoodRx than from rogue and unclassified online pharmacies across all formulations and strengths of Adderall. Rogue and unclassified online pharmacies promoted and enabled the illicit purchase of Adderall,

appealing to privacy (74%), offering purchase through cryptocurrency (74%), and claiming registration or accreditation of their sites (33%).

Insulin

Of the 49 online pharmacies found to sell Humalog or NovoLog, 60% were illegitimate (e.g., rogue or unapproved). From these pharmacies, Humalog and NovoLog were 2-5 times cheaper as compared to legitimate online pharmacies. Risks associated with the use of illegitimate online pharmacies were evident in that, of the online pharmacies that shipped within the U.S. (including rogue and unapproved), 60% did not require a prescription, 47% did not display drug warnings or information, and only 20% offered access to a purported pharmacist.

Conclusion

Illegitimate online pharmacies are pervasive in search engine results, enabling the illicit purchase of Adderall, Humalog, and NovoLog without a prescription. There is concern that patients might purchase these medications from illegitimate online sources—knowingly or not—for perceived ease of access, privacy, lower cost, or other 'perks' that illegitimate online pharmacies claim. Law enforcement, regulatory agencies, healthcare professionals, and search engines should work to further protect consumers from illegitimate online pharmacies selling prescription medications like Adderall and rapid-acting insulins.

Background

Online pharmacies have emerged as a popular destination for the purchase of prescription drugs. Though the overall volume varies on a daily basis, 30,000-35,000 accessible online pharmacy websites were found to be accessible in 2016.[1] Online pharmacies can be defined by whether they operate as legitimate and registered pharmacies or whether they are illegitimate and in violation of U.S. pharmacy laws and practice standards.[2] According to LegitScript, a verification and monitoring service, 96% of all accessible online pharmacies are illegitimate, of which 92% are rogue, meaning that they sell drugs without a valid prescription.[1] Given the high prevalence of rogue online pharmacies, the ease of access to high-risk medications and medications of abuse is of particular concern.

National organizations have been combatting the proliferation of illegitimate online pharmacies. The Food and Drug Administration's (FDA) *BeSafeRx* campaign and the Alliance for Safe Online Pharmacies' (ASOP) '*Buy Safe Rx*' campaign empowers consumers by raising awareness of the dangers of purchasing medications from illegitimate online pharmacies, as well as providing information on the warning signs that an online pharmacy might be operating illegally.[3,4] The National Association of Boards of Pharmacy (NABP) lists accredited digital pharmacies on its website.[5] NABP also offers a verification service for legitimate online pharmacies through which they can receive a '.pharmacy' domain, increasing consumers' visibility of legitimate pharmacies. LegitScript allows consumers to enter a uniform resource location (URL) to determine a pharmacy's legitimacy.[6] Moreover, regulatory and legal actions beyond raising public awareness are ongoing against illegitimate online pharmacies. Operation Pangea, a cooperative effort led by Interpol in conjunction with the FDA and US Department of Justice (DOJ) has led to the removal of thousands of illegitimate online pharmacies.[7] LegitScript has also partnered with the FDA to identify and close illegitimate online pharmacies. Still, illegitimate online pharmacies remain challenging to control, as there are innumerable URLs under which they can operate.

Despite these organizational attempts, illegitimate online pharmacies remain pervasive and many consumers remain unaware of the associated dangers. In choosing illegitimate online pharmacies, consumers opt out of medication counseling, monitoring, and drug-drug interaction checking that pharmacists and healthcare professionals offer.[8] The utilization of such resources in healthcare has been shown to improve patient outcomes.[9] Concerns regarding insufficient safety measures are further exacerbated by the marketing methods that illegitimate online pharmacies use to attract consumers.[10,11] Though it has been shown that patients using no-prescription online pharmacies are at greater risk of developing treatment-related adverse events, there is a lack of current data on how illegitimate online

pharmacies approach patient safety and what marketing methods they employ, particularly for medications of high risk and abuse potential.[12]

Adderall

Adderall (amphetamine/dextroamphetamine) is a central nervous system (CNS) stimulant medication commonly used to treat attention-deficit/hyperactivity disorder (ADHD). Though effective in its treatment of ADHD, Adderall carries a high potential for abuse and dependence—its non-medical use among college students for neurocognitive enhancement has been well-documented, with a prevalence estimated from 9-23%.[13-15] Overall non-medical use of prescription stimulants has been estimated at around 8% in adults.[16] Inherent to the abuse of amphetamines are risks including weight loss, cardiovascular events, psychological dependence, and morphological brain changes.[17-22] Due to its high potential for abuse, which could lead to severe psychological or physical dependence, Adderall is classified by the U.S. Drug Enforcement Administration (DEA) as a schedule II medication.[23]

Insulin

For patients with Type 1 or Type 2 advanced diabetes, insulin is a cornerstone of therapy. One in ten Americans (around 34.2 million people) have diabetes, with nearly 1.6 million living with Type 1 diabetes.[24] Patients with Type 1 diabetes cannot produce endogenous insulin and thus require treatment with exogenous insulin. For patients living with Type 2 diabetes, insulin is often required if they cannot maintain adequate glycemic control with lifestyle modifications and non-insulin medications. In those patients who require insulin, regulation of blood glucose is tantamount to disease control—if uncontrolled, it can result in the acute, life-threatening conditions of diabetic ketoacidosis or severe hypoglycemia, as well as chronic but still life-threatening complications like cardiovascular disease, nephropathies, retinopathies, and neuropathies.[25] These complications can result in—among other outcomes—dialysis-dependence, blindness, amputations, serious quality-of-life reductions, and death.[25]

Increasingly, rising costs unique to the U.S. market have hindered access to insulin for patients.[26] Despite legislative initiatives to control prescription drug costs, high insulin costs in the U.S. persist, with list prices of insulin tripling from 2003 to 2013.[26] While insulin was first used as a medication in 1922, the insulin market remains dominated by branded products, with no actual generic drug approved. Generic competition has been shown to decrease drug prices by 60%, on average, when 3 generic manufacturers are in the market.[27] High costs are associated with all insulin types, but rapid-acting insulin analogues like Humalog (insulin lispro) and NovoLog (insulin aspart) are among the highest priced.[26] Humalog's list price, for example, continued to increase after 2014 from $391 to nearly $600 in 2017—a list price increase similar

to that of its competitor NovoLog. It is worth noting that net prices remained relatively stable for Humalog and NovoLog during that timeframe, meaning increase in costs were primarily offset by discounts made available.[28] Regardless, high list prices have a direct impact on patients—in 2019, 1-in-4 patients in the U.S. with Type 1 diabetes reported difficulties affording their medication.[29] Patients like this are often led to make difficult decisions—in 2019, more than 1-in-4 patients in the U.S. with Type 1 diabetes reported rationing their insulin.[30] Patients who struggle to access insulin from traditional methods, namely brick-and-mortar pharmacies, might look to alternative, lower-cost methods, such as purchasing insulin from friends, across borders, or from illegitimate online pharmacies.[31,32]

The accessibility of Adderall and rapid-acting insulins from illegitimate online sources is a public health hazard. We investigated the availability of these medications from online pharmacies through search results of common search engines and documented the websites' safety and marketing characteristics, as well as costs of Adderall, Humalog, and NovoLog.

Methods

Website selection was conducted from September 2019 to February 2020 using four different search engines (Google, Bing, Yahoo, and DuckDuckGo) with the phrases 'buy Adderall online', 'buy Humalog online', 'buy NovoLog online', and 'buy insulin online'. Two distinct analyses were performed on results for Adderall and results for rapid-acting insulins. The four queried search engines were chosen based on user traffic and, for DuckDuckGo specifically, its emphasis on user privacy. Search algorithms on these websites incorporated synonyms of search terms. The first 100 results of Google and Bing and the first 50 of Yahoo and DuckDuckGo were screened for each medication, incorporating more results from popular search engines. Websites were included if they claimed to sell the queried medication, were active websites, free to access, in English language, and had a unique URL. For Adderall, information for websites selling either Adderall immediate release (IR) or Adderall extended release (XR) were collected, as these products contain the same active ingredient (amphetamine/dextroamphetamine). For Humalog and NovoLog, information for websites selling any formulation (e.g., vials, pens, or cartridges) were collected. Websites that required one extra click to reach the website selling the medication were also included. Screenshots were taken of website pages to ensure the internal validity of results.

The legitimacy of websites was assessed using LegitScript, a verification and monitoring service that has monitored more than 70,000 online pharmacies.[6] Among other criteria, LegitScript classifies pharmacies depending on: licensure or registration in affiliated jurisdictions, sale of controlled substances, prior discipline, requirement of valid prescription, protection of privacy, patient services offered, transparency,

and domain name registration.[33] Websites in this analysis were classified as LegitScript defines them: *rogue*—'these merchants engage in illegal, unsafe, or misleading activities like selling prescription drugs without a prescription'; *unapproved*—'these merchants have some problem with regulatory compliance or risk, but it is typically less egregious than 'rogue', *legitimate*—'these merchants are registered with a LegitScript certification program and have passed LegitScript certification criteria'; or *unclassified*—no information was available from LegitScript.[34] For the analysis of rapid-acting insulins, *rogue* and *unapproved* are often referred to collectively as *illegitimate* online pharmacies.

The average monthly traffic to website domains defined as unique visits from any country was obtained using www.SimilarWeb.com. This website aggregates information on website traffic from a variety of sources including open exchange of first-party data and surveying public data sources. The internet protocol (IP) addresses of websites were checked using www.IP2location.com, which retrieves geographical information based on IP addresses. Registered geographic locations of the IP addresses were compared to listed website locations.

Safety

Characteristics related to safety were selected based on previous literature and obtained from each included website.[2,8,10,35,36] Characteristics were compared across rogue, unclassified, and legitimate online pharmacies. For insulins, to allow for a specific focus on U.S. pharmacies, safety characteristics were analyzed only for online pharmacies that offered shipping within the U.S. For both Adderall and insulins, basic pharmacy-related safety characteristics included the requirement of a prescription, controls on the amount of medication that could be ordered (e.g., restricting patients to a 90-day supply). Characteristics related to pharmacy services included whether there was an offer to speak with a pharmacist, and whether drug information and drug-related warnings and precautions were displayed on the product page. Characteristics related to location included whether the pharmacy listed a physical location and the website location listed vis-à-vis IP address location (and whether it matched the location listed). For Adderall alone, requirement of a health-related questionnaire was also assessed.

Marketing

Characteristics related to marketing were selected based on previous literature.[2,8,10,11,35,36] Marketing characteristics were compared across online pharmacy type. For both Adderall and insulins, cost-related marketing characteristics included whether online pharmacies offered bulk discounts or 'promo codes' on checkout or claimed a 'discount' compared to other pharmacies. Promotional marketing characteristics included whether online pharmacies displayed specific drug advertisements pertaining to any form of

Adderall or insulin, advertisements for other products on the page advertising the queried medication, or customer testimonies. Marketing characteristics appealing to customer service and general reputability included whether online pharmacies displayed a phone number, offered the assistance of an associate, or claimed pharmacy registration in some form (e.g., Canadian International Pharmacy Association (CIPA); International Pharmacy Association of British Columbia (IPABC); etc.). Additional marketing characteristics included whether online pharmacies offered privacy reassurances (e.g., discrete packaging or protection of health- or billing-related information) or offered shipping within the U.S. For Adderall, additional collected marketing characteristics included whether the online pharmacy facilitated purchases using cryptocurrency (e.g., Bitcoin). For insulins, shipping within the U.S. was assessed. In addition, to examine specific marketing language for insulins, we collected text from the homepages of included online pharmacies. After initial inspection to identify the most common marketing language, the text was screened to determine whether the following characteristics were discussed: (i) quality; (ii) safety; (iii) customer service; (iv) reputability; (v) affordability; and (vi) convenience. These characteristics were defined and quotes representative of each characteristic and pharmacy type were collected.

Cost

Price and shipping costs of Adderall IR and Adderall XR 30 mg at the most frequently sold quantities of 60, 90, 120, 180, and 240 were collected. Price per tablet or capsule of Adderall IR and Adderall XR were calculated accounting for shipping costs. For Adderall, shipping costs were distributed among the total quantity of pills or capsules in an order. Costs of Humalog and NovoLog 100 IU/mL insulin at the most frequently sold dosage forms (i.e., 1x10 mL vials, 5x3 mL pens, 5x3 mL cartridges) were collected form online pharmacies that offered to ship within the U.S. Price per mL of 100 IU/mL Humalog and NovoLog for vials, pens, and cartridges was calculated. For insulins, shipping costs and bulk discounts were not considered in the cost calculations. For both Adderall and insulins, online pharmacy prices were compared to prices offered through GoodRx, an online prescription drug coupon site, which is what a U.S. consumer might expect to pay out-of-pocket without insurance at a brick-and-mortar store.[37]

Results

Adderall

Through searching Google, Bing, Yahoo, and DuckDuckGo with the query 'buy Adderall online,' we identified a total of 62 online pharmacies claiming to sell Adderall (Figure 1). Of these online pharmacies, LegitScript classified 50 as rogue, while 11 were unclassified (i.e., no information about those sites were available through LegitScript), and 1 site was legitimate. Traffic to these websites, as determined by www.SimilarWeb.com, differed depending on classification as outlined in Figure 2. The traffic to rogue

and unclassified websites was low, with the majority receiving <5000 unique monthly visits. Monthly traffic of the one legitimate website was comparatively much larger at 1-2 million unique monthly visits.

Safety characteristics of all online pharmacies selling Adderall are described in Table 1. Among rogue and unclassified pharmacies, prescriptions and health-related questionnaires were not required (100%), none offered pharmacist services (100%), and none placed a quantity limit on the number of Adderall that could be ordered (100%). Rogue and unclassified pharmacies commonly offered some form of drug warning/precautions (64%), and nearly uniformly provided some form of drug information (89%). The location of rogue and unclassified online pharmacies was not listed on nearly half (49%) of their websites. Overall, the locations listed on rogue and unclassified online pharmacy websites were not consistent with the locations of their servers as determined by www.IPLocation.net (80%). Server locations and respective website-listed locations of online pharmacies in our sample are depicted in Figure 3.

Marketing characteristics of all online pharmacies selling Adderall are described in Table 2. Rogue and unclassified online pharmacies often made cost arguments by claiming a price discount compared to other pharmacies (61%), providing bulk discounts (67%), and offering coupon on promotion codes (70%). Other marketing characteristics included the use of advertisements in various forms: customer testimonies (66%); Adderall-specific ads (31%); and ads for other products on the product page (84%). Rogue and unclassified online pharmacies stressed their accessibility by offering a phone number or WhatsApp contact information (82%), and nearly uniformly offered customers to speak with an associate through a 'Contact Us' page or chat feature (98%). Privacy was stressed – rogue and unclassified online pharmacies provided privacy assurances on either patient information or 'discreet package delivery' (74%). Privacy was also offered by accepting cryptocurrency such as Bitcoins (74%). Rogue and unclassified online pharmacies often declared some form of registration or verification through varied accrediting bodies and agencies such as the PCCA or NABP Digital Pharmacy Accreditation, in turn suggesting product quality and safety (33%).

For rogue and unclassified online pharmacies, the cost per tablet of Adderall IR and cost per capsule of Adderall XR at quantities of 60, 90, 120, 180, and 240 are displayed in Figure 4. At all quantities, prices for Adderall IR and Adderall XR online were greater than the price offered through the coupon site GoodRx.

The singe legitimate website (www.humanapharmacy.com) required a prescription, offered pharmacist services, and placed a limit on quantity of Adderall that could be sold, as determined by the quantity written on the prescription. Drug warnings/precautions, drug information, and price for Adderall could not be observed on this site because consumers were unable to advance without a member ID and prescription.

The marketing characteristics of the legitimate website did not place an emphasis on price (there were no listed price or bulk discounts) but did emphasize accessibility with a phone number listed and an offer to speak with an associate. The legitimate website offered privacy assurances and advertised its registration and accreditation with NABP, Utilization Review Accreditation Commission (URAC), and Accreditation Commission for Health Care (ACHC).

Insulin

We screened 300 websites and identified a total of 49 online pharmacies that claimed to sell Humalog or NovoLog (Figure 5). Of the online pharmacies, LegitScript classified 29 (59%) as illegitimate (18 (37%) rogue and 11 (22%) unapproved) and 7 (14%) as legitimate, while 13 (27%) were unclassified. The listed location of these online pharmacies differed, with 12 illegitimate online pharmacies (rogue N=12; unapproved N=0) that advertised no location. Of the 29 illegitimate online pharmacies, 15 advertised a Canadian location (rogue N=4; unapproved N=11). The remaining illegitimate online pharmacies claimed a Great Britain (N=1), Europe (N=1) location. No illegitimate online pharmacies advertised a US location. For legitimate online pharmacies, 3 advertised locations in the U.S., 2 in Australia, 1 in Canada, and 1 in India. Physical locations listed on websites were compared to server locations, as determined by www.IPLocation.net. All legitimate online pharmacies' physical locations listed on their websites matched that of their server locations. Whereas, illegitimate online pharmacies classified as unapproved had a matching physical and server location 40% of the time, while illegitimate online pharmacies classified as rogue had no matching physical to server locations.

Traffic to online pharmacies, as determined by www.SimilarWeb.com, differed depending on classification. Though illegitimate online pharmacies were the most abundant online pharmacy type in the search results, unique monthly visits were comparatively lower to illegitimate online pharmacies (0 to 250,000) than to legitimate online pharmacies (5000 to 63.6 M). The 3 U.S.-based legitimate online pharmacies received the highest volumes of unique monthly traffic—1.17 M (healthwarehouse.com), 40.35 M (cvs.com), and 63.6 M (costco.com).

Safety characteristics of online pharmacies selling Humalog and NovoLog within the U.S. are described in Table 3. Rogue online pharmacies differed from legitimate online pharmacies more substantially than unapproved online pharmacies. Rogue online pharmacies seldom required a prescription (10%) or placed quantity limits on amount of medication ordered (10%), and none offered pharmacist services (0%). Unapproved online pharmacies uniformly claimed to require a prescription (100%) and placed quantity limits (100%), and some sites offered pharmacist services (60%). For both rogue and unapproved online

pharmacies, drug-related warnings and information were not uniformly displayed. Though data was unavailable for one legitimate online pharmacy regarding whether pharmacist services were offered (a member registration was required), and not all legitimate online pharmacies were accredited through the NABP due to geography, legitimate online pharmacies required or displayed characteristics consistent with best online pharmacy communication practices such as requiring pharmacists to offer interactive, meaningful consultation.[5]

Marketing characteristics of online pharmacies selling Humalog and NovoLog are described in Table 4. Rogue online pharmacies differed from unapproved and legitimate online pharmacies in several characteristics—more often, they offered bulk discounts (61%), assured privacy (78%), and promoted other products on the Humalog® or NovoLog® insulin product page (72%). Though rogue online pharmacies offered some form of contact through e-mail or a chat function, a majority did not offer a phone number (61%). Both legitimate and unapproved online pharmacies shared similar characteristics—few offered bulk discounts (29% legitimate; 18% unapproved), all displayed a phone number (100%), and most touted registration or accreditation claims (86% legitimate; 91% unapproved).

Marketing language from website homepages differed among online pharmacy type for certain characteristics—83% of illegitimate online pharmacies appealed to quality (vs 29% of legitimate), safety 66% vs 14%, and customer service 83% vs 57%, respectively. The marketing language was similar among reputability (55% vs 57%), affordability (83% vs 71%), and convenience (76% vs 71%). Differences in marketing language were quantified and demonstrated with select quotes in Table 5. The advertising language of illegitimate online pharmacies tended to communicate an urgency of purchase and emphasized the merits of the pharmacy. For example, one quote from an illegitimate online pharmacy appealed to reputability, affordability, and safety:

> "If you are looking to buy your prescription drugs in Canada, through a reputable international or online Canadian pharmacy, [our online pharmacy] provides you access to a trusted source of affordable and safe prescription drugs."

The costs of Humalog and NovoLog vials, pens, and cartridges were observed for online pharmacies shipping within the U.S. (N=23 including unclassified online pharmacies). The most common volume and strength of insulin vials was 10 mL at 100 IU/mL. Humalog and NovoLog 3 mL pens and 3 mL cartridges were most often sold in packages containing a quantity of 5, which is in alignment with product packaging available from brick-and-mortar pharmacies. Cost per mL of 100 IU/mL insulin varied depending on the

type of online pharmacy. For rogue online pharmacies, the cost of insulin varied depending on dosage form: Humalog vials $11.30 (N=1), Humalog pens $7.84 (N=4), Humalog cartridges $10.04 (N=4), NovoLog vials $5.90 (N=2), NovoLog pens $7.69 (N=8), NovoLog cartridges $8.00 (N=3). Costs were similarly low-cost in unapproved and unclassified online pharmacies. For legitimate online pharmacies, the cost of insulin (without insurance) was 2-5-fold higher depending on dosage form: Humalog vials $31.51 (N=2), Humalog pens $38.89 (N=2), Humalog cartridges (N=0), NovoLog vials $32.77 (N=2), NovoLog pens $40.77 (N=2), NovoLog cartridges $38.47 (N=2). Compared to illegitimate pharmacies, GoodRx costs were also approximately 2-5 times more expensive, whereas compared to the cost from legitimate pharmacies (for uninsured patients), GoodRx prices were marginally cheaper: Humalog vials $17.22, Humalog pens $21.83, Humalog cartridges $34.13, NovoLog vials $29.38, NovoLog pens $37.31, NovoLog cartridges $35.90. The difference in cost per mL of Humalog and NovoLog pens (the most common dosage form in our analysis) depending on source is depicted in Figure 6.

Discussion

Adderall

We found that the vast majority of online pharmacies selling Adderall were rogue or unclassified by LegitScript. Of 62 online pharmacies claiming to sell Adderall, only one was a legitimate seller. By not requiring a prescription, rogue pharmacies allow the purchase of medications that could be abused, enabling the ill-advised practice of Adderall use without concurrent therapeutic monitoring.

With high doses and repeated use of Adderall, the development of psychological amphetamine dependence and adverse events such as weight loss, psychosis, seizures, and cardiovascular events can occur.[17,18] Though data is sparse, morphological brain changes and related behavioral alterations—particularly in adolescents with prolonged amphetamine use—are also a concern.[19-21] In addition, though we did not conduct an analysis on drug quality, it is documented that illegitimate online pharmacies frequently sell substandard and falsified medications.[36] Consumers with and without valid prescriptions face risks when purchasing from illegitimate online pharmacies. Those with a valid prescription might receive poor quality medication and be harmed by impurities, fail to achieve therapeutic goals, and suffer from a lack of therapeutic monitoring. Those without a valid prescription, who might be more inclined to abuse Adderall and take more than the necessary dose, are predisposed to the same risks as those with a prescription, as well as the potential for an increased frequency of dose-dependent adverse effects.

Concerns related to the purchase of Adderall from rogue online pharmacies are amplified by the marketing characteristics that these pharmacies employ. As evinced in these pharmacies not placing quantity limits on

the amount of Adderall for purchase, rogue online pharmacies intend to sell as much of these products as possible. The sale of Adderall is achieved through varied selling arguments—the appeal to cost-savings, constant customer support, and privacy, which are perhaps the most important selling arguments for consumers who intend to purchase controlled substances without a prescription. Rogue online pharmacies in the sample appealed to discrete package delivery, protection of patient information, and the use of de-identified forms of payments involving cryptocurrency. These selling arguments, which are designed to lure consumers into purchasing more medications, run counter to reasonable patient care and sensible legislation that aims to protect the public from drugs of abuse and misuse.

Previous studies comparing prescription drug prices between online and brick-and-mortar pharmacies have had mixed results depending primarily on the drug studied, with several finding lower costs online.[38,39] Our investigation into the cost of Adderall IR and Adderall XR from rogue online pharmacies revealed that marketing language detailing 'affordability' was not necessarily true for the purchase of Adderall without a prescription. Compared to prices listed on GoodRx, a popular coupon site for patients purchasing medications without insurance, rogue online pharmacy prices including shipping costs for Adderall IR and Adderall XR were nearly 5-fold more expensive per unit. The steep price differential is suggestive of the illegal nature of Adderall purchase without a prescription online. From a cost standpoint, patients with a valid prescription have little incentive to purchase Adderall from a rogue online pharmacy. This result supports existing literature that among online pharmacies, there is a price markup for the purchase of medications without a prescription.[11] Our results demonstrate that the no-prescription price differential extends to brick-and-mortar pharmacies, which offer cheaper medications.

Unfortunately, despite governmental and organizational attempts to quell their proliferation, rogue online pharmacies are challenging to control as they regularly re-emerge. Though the overall web traffic to rogue online pharmacies in our results was relatively low (Figure 2), this could be suggestive of the methods that rogue online pharmacies use to avoid detection, regularly closing and opening new websites under unique URLs. This is supported by our finding that geographic locations listed on rogue and unclassified online pharmacy websites were largely (80%) not consistent with locations of their servers. These results demonstrate that search engines are not effectively screening for and removing rogue online pharmacies from their search results at present. In the absence of efficient methods to regulate and remove rogue online pharmacies, it is imperative that search engines acknowledge the pervasiveness of rogue online pharmacies within their search results and take additional measures of control. Search engines should help lead the effort to create a safer online pharmacy landscape through the generation of search algorithms that select for legitimate online pharmacies.

Insulin

Our analysis demonstrates that both Humalog and NovoLog are readily available from online pharmacies that engage in the illegal sale of prescription drugs. Illegitimate (i.e., rogue and unapproved) online pharmacies were abundant in the results of common search engines, outnumbering the legitimate online pharmacies. Of the unique online pharmacies that we included in our analysis, nearly 60% were illegitimate, while only 14% were legitimate (with the remainder being unclassified). The relative prevalence of illegitimate online pharmacies poses a threat to unsuspecting consumers and provides easy access to those seeking insulin without a prescription.[32] The incentive to purchase insulin from illegitimate online pharmacies goes beyond ease of access, as our analysis reveals that these online pharmacies offer substantial price reductions as compared to brick-and-mortar and legitimate online pharmacies.

In the U.S., rising list prices on rapid-acting insulin analogues like Humalog and NovoLog have resulted in substantial cost burdens for patients with diabetes. Legislative initiatives to curb insulin costs include, among others, out-of-pocket maximums and personal drug importation. However, these reforms have only been trialed on the state level and not federally, and the legality of personal importation of insulin remains contentious.[40,41] In 2018, in the midst of public outcry at high insulin costs, the manufacturer Eli Lilly introduced Lispro, an authorized generic to Humalog, at a 50% discount to the Humalog list price.[42] Unfortunately, according to a Senate report, the uptake of Lispro has been meager at best, with 83% of 386 surveyed national pharmacies not having Lispro in stock and 69% unable to order the drug.[43] In 2020, the Trump Administration announced that Medicare would begin offering 1,750 insurance plans that capped out-of-pocket spending to $35 for insulin.[44] However, this out-of-pocket maximum is limited to Medicare beneficiaries. Given relatively limited action from the federal government, manufacturers, and other key players in the U.S. pharmaceutical supply chain, high insulin list prices and out-of-pocket costs for many persist, and patients continue to have access problems, particularly those who are uninsured—which in 2018 made up 8.5% of the U.S. population—or have a high deductible insurance plan.[26,45]

With financial pressures, patients who require insulin to manage their diabetes have resorted to illegal activities such as borrowing insulin, importing insulin from lower-cost countries, or purchasing insulin from illegitimate online sources.[31] Our analysis, which focuses on the online pharmacy marketplace, demonstrates that among pharmacies that ship within the U.S., the cost of Humalog and NovoLog per mL from illegitimate online pharmacies (depending on product and dosage form) is approximately 2-5 times cheaper than that offered from legitimate online pharmacies or GoodRx, as outlined in Figure 6. These substantial price differences raise concerns that illegitimate online pharmacies might appeal to patients

priced out of traditional means of acquiring insulin. Thus, potentially making drastically lower insulin prices a useful indicator of pharmacy legitimacy. Beyond offering lower prices, rogue online pharmacies also employ marketing methods that might appeal to a cost-conscious consumer such as offering bulk discounts or coupons, as seen in Table 4. In addition, illegitimate pharmacies appeal to affordability through language on their homepages, as detailed in Table 5.

Though costs are lower for Humalog and NovoLog from illegitimate online pharmacies, they remain illegal because there are serious risks associated with their use. Humalog and NovoLog are high-risk medications that require both therapeutic monitoring to ensure optimal short- and long-term outcomes and sufficient counseling for the prevention of adverse events like hypoglycemia. From 2007-2009, nearly 20% of emergency hospitalizations for treatment of emergent adverse events were due to insulin.[46] The cost of these visits is not trivial—in 2016, the total mean cost per-person per-visit for hypoglycemia was $1,965 for an emergency department (ED) visit and $11,632 for an inpatient hospitalization.[47] The American Diabetes Association (ADA) recommends that patients treated with insulin who are unaware of hypoglycemia should be counseled on signs and methods to treat.[48]

Our analysis demonstrates that illegitimate online pharmacies—particularly rogue online pharmacies—do not offer pharmacy services on-par with those offered through legitimate online pharmacies, as outlined in Table 3. 90% of rogue online pharmacies that shipped within the U.S. allowed the purchase of Humalog or NovoLog without a prescription, precluding the involvement of healthcare professionals in patient care. Further preventing communication with healthcare professionals, no rogue online pharmacies made the offer to speak with a pharmacist. On rogue and unapproved online pharmacies, patients were often left without drug information and drug-related warnings and precautions (40% and 60% for both categories, respectively). Given these characteristics, illegitimate online pharmacies—with rogue online pharmacies being the worst offender—allow patients to access Humalog and NovoLog with minimal information, predisposing these patients to poor diabetes control and the potential development of adverse events.

Limitations

There were several limitations to our study. We limited our screening to 300 websites for each medication due to feasibility. Given this limitation, numerous online pharmacies remained undetected. This limited screening yielded, in the Adderall analysis, only one legitimate pharmacy, and in the insulin analysis, only three legitimate pharmacies that shipped within the U.S., precluding an in-depth analysis comparing the characteristics of rogue versus legitimate pharmacies. However, we believe that our methodology accurately replicates the behavior of a typical U.S. consumer who would only view the first few pages of

search results. Though we were able to assess how many unique visits each online pharmacy received from www.SimilarWeb.com, it is not possible to determine how frequently the medications were viewed or purchased on each website. We did not attempt to purchase the medications from any of the included online pharmacies. It is therefore unclear whether an order placed with an online pharmacy included in this sample would have resulted in the delivery of the medication. Without purchasing the product, we also could not test the quality of the medication. However, we believe that the purchase of prescription drugs from rogue online pharmacies is in itself ethically tenuous. Though we believe our results are generally applicable to the online pharmacy landscape, given the transient nature of online pharmacies, our results—in terms of particular sites analyzed—are a slice-in-time, analyzing the sites listed on four search engines in the U.S. from September 2019 to February 2020. Our study also failed to capture the prevalence of medication advertising on social media platforms, which is an emerging market for the advertising and person-to-person sale of prescription drugs.[49,50] Still, we hold that common search engines remain a relevant and easy access point for consumers to access websites selling controlled substances. Finally, data collection for our study was conducted prior to the COVID-19 pandemic, which saw an increase in rogue online pharmacies peddling no-prescription medications, particularly for treatment of COVID-19.[51] Our results remain relevant and particularly important as online consumption of goods and prescription medications becomes commonplace, putting more consumers at risk to purchase from rogue online pharmacies.

Conclusion

Adderall, a controlled substance with high potential for abuse, and rapid-acting insulins, a high-risk class of medications, are readily accessible online without a prescription. While doing little to assure patient safety, illegitimate online pharmacies treat patients as consumers with aggressive marketing tactics. The relatively low cost of rapid-acting insulins places patients purchasing these medications at an even higher risk. Governmental agencies should continue to pursue legal and regulatory pressures with the intent to close illegitimate online pharmacies. Search engines should work to better filter their results, decreasing visibility of illegitimate online pharmacies. Finally, while public awareness campaigns and provider-to-patient efforts can bring attention to the dangers of illegitimate online pharmacies, they do not address the reasons that patients might visit these sites. With patient safety in mind, legislators and members of the pharmaceutical supply chain should work to lower the cost of insulin, in effect diminishing patients' incentive to purchase from illegitimate online pharmacies.

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Figure and Tables

Figure 1 (Adderall). Search strategy used to collect online pharmacies selling Adderall

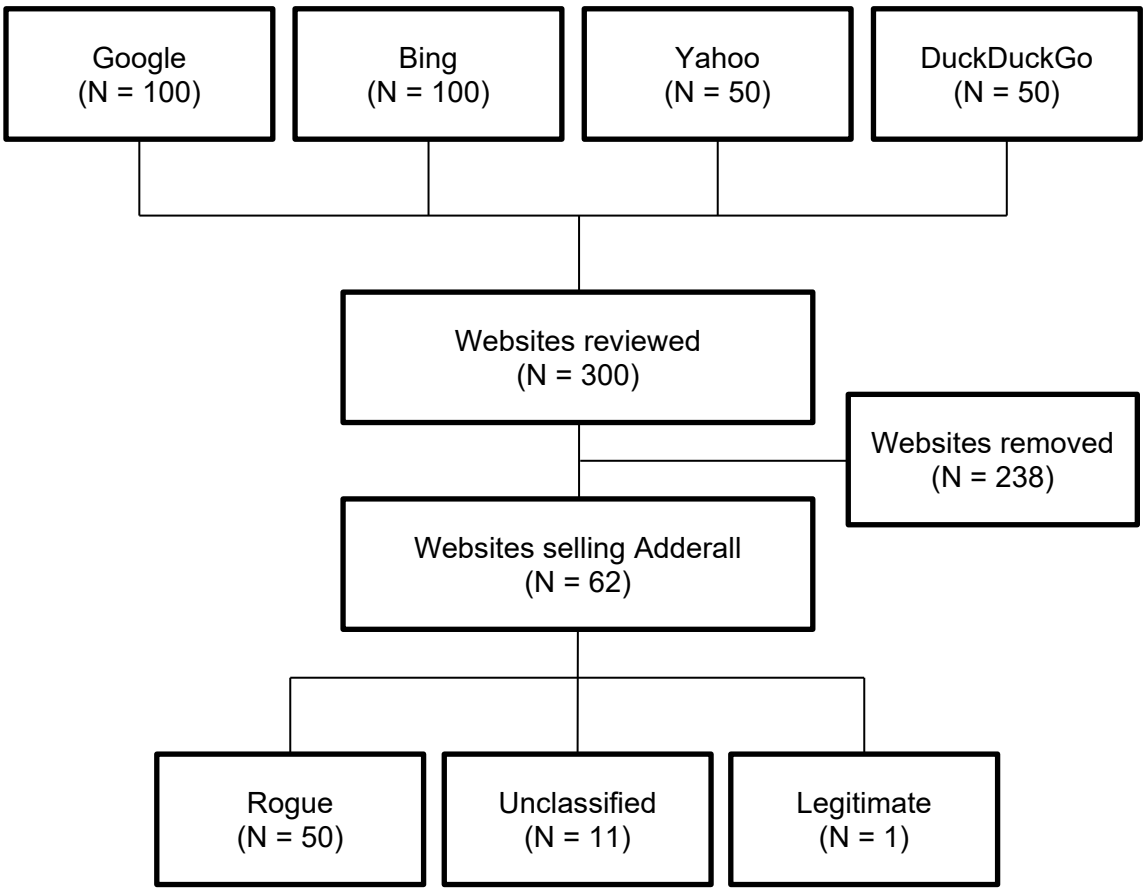
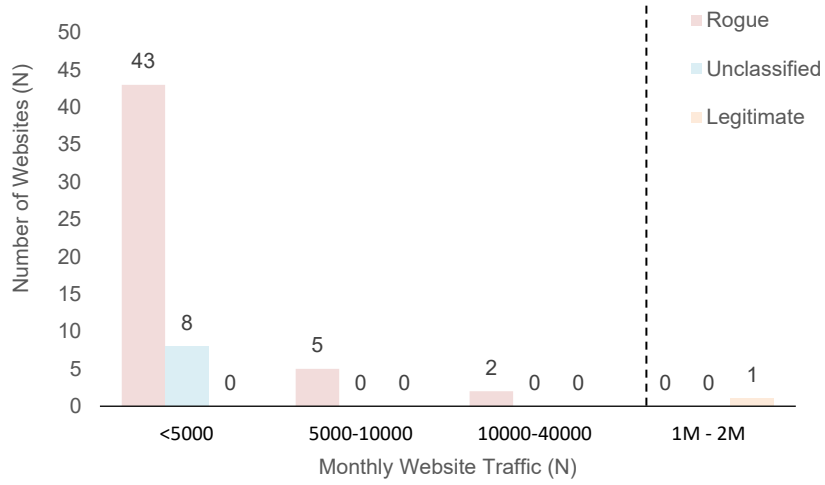


Figure 2 (Adderall). Monthly website traffic (unique visits) to online pharmacies selling Adderall



Key: M—million, N—number

* Three *unclassified* results had no information regarding website traffic

Table 1 (Adderall). Safety characteristics of online pharmacies selling Adderall stratified by rogue, unclassified, and legitimate pharmacies

	Rogue (N = 50)		Unclassified (N = 11)			Legitimate (N = 1)		
	Yes	No	Yes	No	NR	Yes	No	NR
Prescription required	0	50 (100%)	0	11 (100%)	0	1 (100%)	0	0
Health-related Questionnaire required	0	50 (100%)	0	11 (100%)	0	0	1 (100%)	0
Offer to speak with RPh	0	50 (100%)	0	11 (100%)	0	1 (100%)	0	0
Drug precautions on product page	33 (66%)	17 (34%)	6 (55%)	4 (36%)	1 (9%)	0	0	1 (100%)
Drug information on product page	45 (90%)	5 (10%)	9 (82%)	1 (9%)	1 (9%)	0	0	1 (100%)
Quantity control	0	50 (100%)	0	11 (100%)	0	1 (100%)	0	0
Location listed on website and location of server match	8 (16%)	42 (84%)	4 (36%)	7 (64%)	0	1 (100%)	0	0

Key: N—number, NR—not reported, RPh—pharmacist

Figure 3 (Adderall). Rogue online pharmacies selling Adderall had server locations that seldom matched those claimed on the website

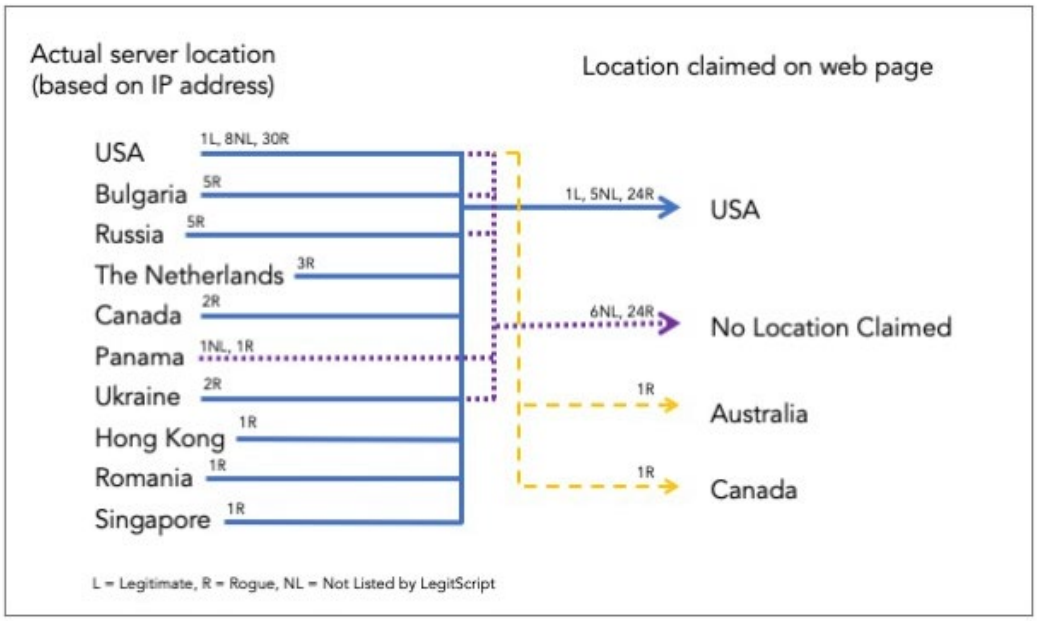
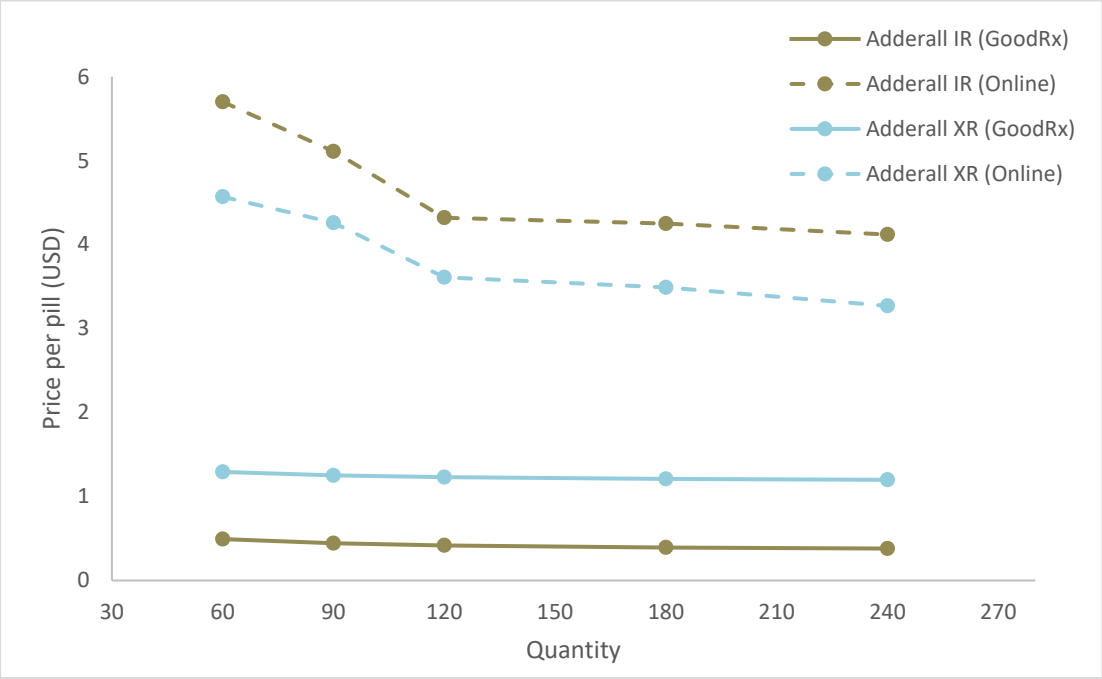


Table 2 (Adderall). Marketing characteristics of online pharmacies selling Adderall stratified by rogue, unclassified, and legitimate pharmacies

	Rogue (N = 50)		Unclassified (N = 11)			Legitimate (N = 1)		
	Yes	No	Yes	No	NR	Yes	No	NR
Claims price discount	31 (62%)	19 (38%)	6 (55%)	5 (45%)	0	0	1 (100%)	0
Bulk discounts	34 (68%)	16 (32%)	7 (64%)	4 (36%)	0	0	1 (100%)	0
Coupon or promo code	35 (70%)	15 (30%)	8 (73%)	3 (27%)	0	0	0	1 (100%)
Accepts cryptocurrency	37 (74%)	13 (26%)	8 (73%)	2 (18%)	1 (9%)	0	1 (100%)	0
Adderall-specific ads	15 (30%)	35 (70%)	4 (36%)	7 (64%)	0	0	1 (100%)	0
Ads for other products on page selling Adderall	43 (86%)	7 (14%)	8 (73%)	2 (18%)	1 (9%)	0	0	1 (100%)
Phone # or WhatsApp	41 (82%)	9 (18%)	9 (82%)	2 (18%)	0	1 (100%)	0	0
Offer to speak with associate	49 (98%)	1 (2%)	11 (100%)	0	0	1 (100%)	0	0
Registration claims	15 (30%)	35 (70%)	5 (45%)	6 (55%)	0	1 (100%)	0	0
Customer testimonies	35 (70%)	15 (30%)	5 (45%)	6 (55%)	0	0	1 (100%)	0
Privacy assurances	37 (74%)	13 (26%)	8 (73%)	3 (27%)	0	1 (100%)	0	0

Key: N—number, NR—not reported

Figure 4 (Adderall). Price per unit for Adderall IR and XR online compared with GoodRx costs



Key: IR – immediate release, XR – extended release

Figure 5 (Insulin). Search strategy used to collect online pharmacies selling rapid-acting insulins

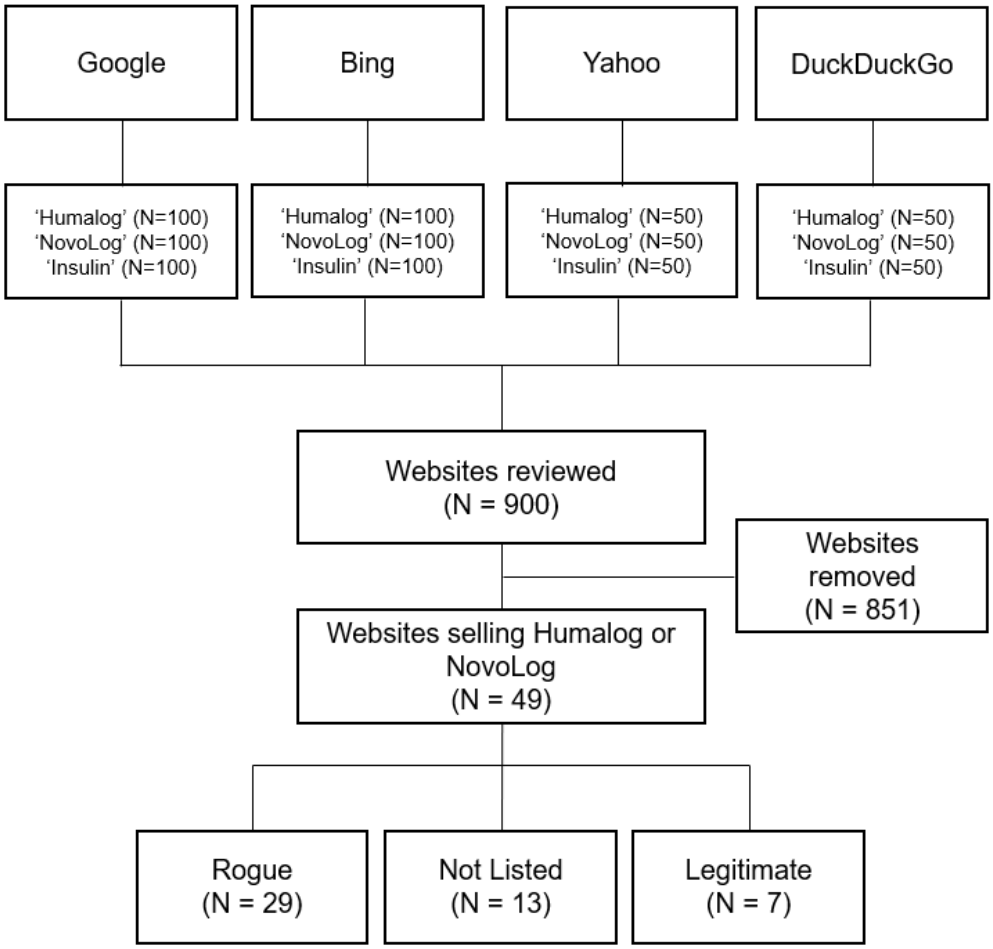


Table 3 (Insulin). Safety characteristics of online pharmacies selling Humalog or NovoLog in the U.S.

	Rogue (N = 10)			Unapproved (N = 5)			Legitimate (N = 3)		
	Yes	No	Not Reported	Yes	No	Not Reported	Yes	No	Not Reported
Prescription required	1 (10%)	9 (90%)	0	5 (100%)	0	0	3 (100%)	0	0
Offer to speak with pharmacist	0	10 (100%)	0	3 (60%)	2 (40%)	0	2 (67%)	0	1 (33%)[a]
Drug precautions on product page	6 (60%)	4 (40%)	0	2 (40%)	3 (60%)	0	3 (100%)	0	0
Drug information on product page	6 (60%)	4 (40%)	0	2 (40%)	3 (60%)	0	3 (100%)	0	0
Quantity control	1 (10%)	9 (90%)	0	5 (100%)	0	0	3 (100%)	0	0
Lists a physical location	3 (30%)	7 (70%)	0	5 (100%)	0	0	3 (100%)	0	0
Location listed on website and location of server match	0	10 (100%)	0	2 (40%)	3 (60%)	0	3 (100%)	0	0

[a] One legitimate pharmacy required an account to gain access to services

Five online pharmacies selling Humalog or NovoLog in the U.S. were not classified by LegitScript.

Table 4 (Insulin). Marketing characteristics of online pharmacies selling Humalog or NovoLog

	Rogue (N = 18)			Unapproved (N = 11)			Legitimate (N = 7)		
	Yes	No	Not Reported	Yes	No	Not Reported	Yes	No	Not Reported
U.S. shipping of insulin	10 (56%)	8 (44%)	0	5 (45%)	6 (55%)	0	3 (43%)	4 (57%)	0
Bulk discounts	11 (61%)	5 (28%)	2 (11%)	2 (18%)	8 (73%)	1 (9%)	2 (29%)	5 (71%)	0
Coupons	9 (50%)	8 (44%)	1 (6%)	2 (18%)	9 (82%)	0	4 (57%)	3 (43%)	0
Registration claims	8 (44%)	10 (56%)	0	10 (91%)	1 (9%)	0	6 (86%)	1 (14%)	0
Privacy assurances	14 (78%)	4 (22%)	0	8 (73%)	3 (27%)	0	1 (14%)	6 (86%)	0
Customer testimonies	10 (56%)	8 (44%)	0	7 (64%)	4 (36%)	0	3 (43%)	4 (57%)	0
Offer to speak with associate	18 (100%)	0	0	9 (82%)	2 (18%)	0	6 (86%)	1 (14%)	0
Phone number	7 (39%)	11 (61%)	0	11 (100%)	0	0	7 (100%)	0	0
Insulin-specific ads	0	18 (100%)	0	3 (27%)	8 (73%)	0	0	7 (100%)	0
Ads for other products on page selling insulin	13 (72%)	5 (28%)	0	1 (9%)	10 (91%)	0	4 (57%)	1 (14%)	2 (29%)

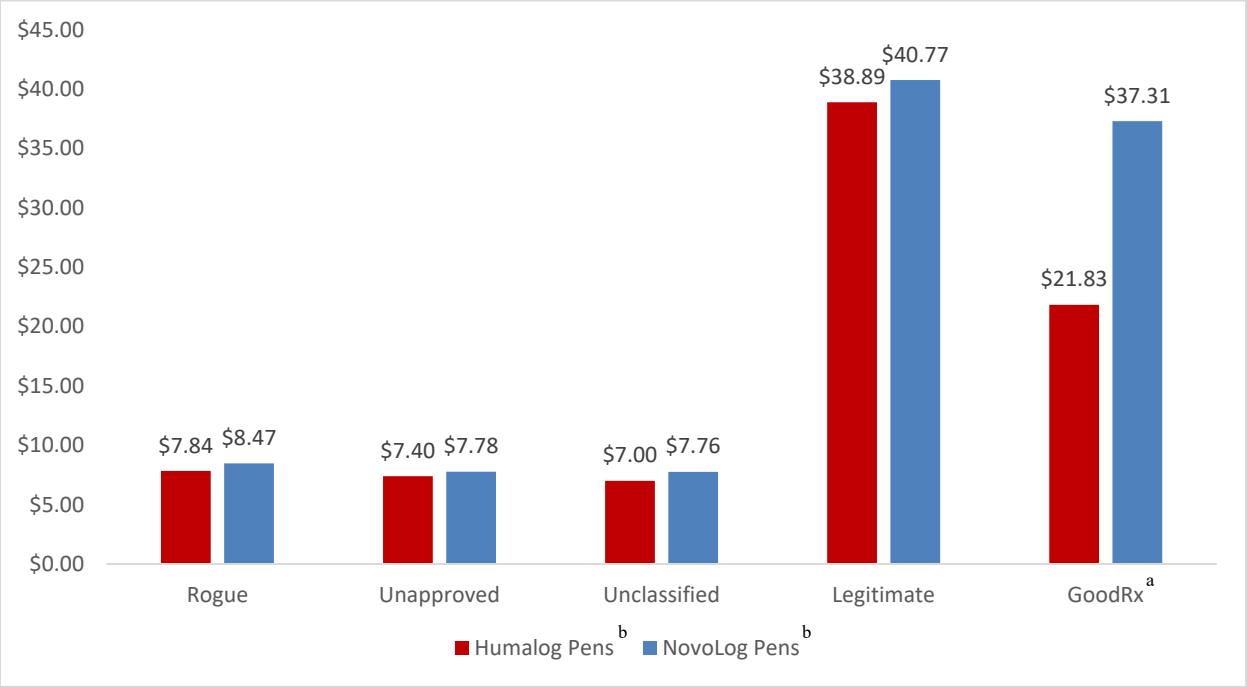
Illustrates marketing characteristics of 49 websites selling Humalog or Novolog.
Thirteen online pharmacies selling Humalog or NovoLog were not classified by LegitScript.

Table 5 (Insulin). Types of marketing language used on 'Home Page' of online pharmacies selling Humalog or NovoLog

Characteristic	Descriptor	Illegitimate (N=29)		Legitimate (N=7)	
		No. (%)	Selected Quote	No. (%)	Selected Quote
Quality	Language suggesting quality of medication or services	24 (83%)	"We guarantee that all [medications] for sale on this site are 100% genuine and extremely powerful."	2 (29%)	"[We] offer you quality care…"
Safety	Language explicitly referring to the safety of drug products, online ordering platform, or other services	19 (66%)	"When it comes to your health, we know that safety is your number one concern. It's ours too."	1 (14%)	"Besides delivering medicines at your doorstep, we…help people use their medicines effectively and safely."
Customer service	Language suggesting availability of staff to answer questions or remedy problems	24 (83%)	"24/7 customer support (we are always at your disposal!)."	4 (57%)	"Customer service: get answers to your questions."
Reputability	Language suggesting renown in selling or accreditation to sell prescription drugs	16 (55%)	"[Our pharmacy] has a great reputation serving the community for 47 years and counting."	4 (57%)	"Accredited & Certified in all 50 states."
Affordability	Language suggesting discounts or cheap prescription drugs	24 (83%)	"[We] provide the same insulin that's available in the US except our prices are much lower, and we pass on the savings to you."	5 (71%)	"At [our pharmacy], you can buy health products and medicines online at best discounts."
Convenience	Language suggesting ease of online pharmacy use or prescription drug purchase; fast delivery or services that allow for time-saving	22 (76%)	"The process of payment through Bitcoin is simple. You need to go through only a few steps to quickly confirm and complete your order."	5 (71%)	"You get the convenience of online shopping combined with the support and guidance of our dedicated team."

Quotes were taken from online pharmacy websites.

Figure 6 (Insulin). Cost of Humalog and NovoLog pens in the U.S. varies depending on source



[a] Prices obtained from GoodRx.com on April 30, 2020.

[b] Costs averaged at each classification for Humalog pens (rogue N=4; unapproved N=4; unclassified N=3; legitimate N=2) and NovoLog pens (rogue N=7; unapproved N=4; unclassified N=3; legitimate N=2).